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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/436,184	11/08/1999	JACK R. WANDS	04930/032001	6241

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	PAPER NUMBER
1643	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	04/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/436,184	WANDS	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *10,13-15 and 39-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *10,13-15 and 39-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/3/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 10, 72 and 74 have been amended. Claims 10, 13-15, 39-76 are pending and under consideration.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 10, 13, 14, 15, 39-42, 72 and 74-76 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 10, 13, 14, 15, 39-42 and 73 are method claims reliant upon the identity of 5' regulatory regions of SEQ ID NO:3. The sequence of SEQ ID NO:3 is a coding sequence. There is no nexus between a coding sequence and a regulatory sequence, because the information in a coding sequence cannot be used to determine the sequence of a regulatory region. As stated in the previous Office action, a statement that the invention includes anti-sense nucleic acids complementary to the 5' regulatory regions of HAAH and a signal peptide is insufficient to describe said regulatory region.

Applicant has amended the claims to recite the putative regulatory region, however the 11-mer is not disclosed in the specification as a regulatory region.. Accordingly the claims are now rejected for the incorporation of new matter. Applicant argues that the regulatory region is disclosed in GenBank SS83325. This has been considered but not found persuasive. The S83325 record discloses the coding sequence but does not disclose a regulatory region.

The rejection of Claims 10, 13-15, 39-50, 72-76 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.
The instant claims have been amended to be dependent upon the coding sequence of SEQ ID NO:2 or the 5' regulatory region of SEQ ID NO:3, both of which are human sequences. Applicant has provided a declaration by Jack Wands averring that three different anti-sense constructs which fall under the scope of the amended claims reduced HAAH expression and inhibited tumor growth in vivo. This has been considered but not found persuasive. The instant claims are directed to the anti-sense modulation of the human AAH, and read on the inhibition of tumor growth in a human patient by the administration of a nucleic acid vector which transcribes a polynucleotide which is complementary of the HAAH regulatory coding sequence which is not disclosed. In the event that the claims were drawn to encompass a complementary coding region within SEQ ID NO:3, the specification is not enabling for the claims requiring the inhibition of tumor growth in a mammal, which reads on the treatment of a human patient with a naturally occurring tumor for the following reasons.

Anti-sense therapy requires uptake of the administered polynucleotide by the target tumor cells. The specification does not provide dosage or data for administering a therapeutically effective dosage of the complementary sequences of the regulatory regions of SEQ ID NO:3, or SEQ ID NO:3 itself, to tumor cells which would result in the inhibition of growth, reproduction or survival of cancer cells. It is noted that many anti-sense therapies which appear to be promising using transfection in vitro, fail to provide any therapeutic efficacy when administered in vivo. For instance, Tolcher et al (Clinical Cancer Research, 2002, Vol. 8, pp. 2530-2535) teach that the administration of the anti-sense oligonucleotides ISIS 3521 and 5132 did not possess clinically significant single agent anti-tumor activity in patients having hormone-refractory prostate cancer, although said oligonucleotides were active inhuman tumor models (page 2533, second column, first paragraph under the heading "Discussion"); Cripps et al (Clinical Cancer Research. 2002, 8, pp. 2188-2192) teach that the same oligonucleotides evoked no clinical response in patients having metastatic colorectal cancer. Cripps et al note that although the steady state plasma levels for both oligonucleotide were above the IC50 for inhibition of mRNA expression, these levels may not have been achieved in the target tissue. Cripps et al also contemplate that additional reasons for the lack of efficacy can be that the target

RNA was not important for the particular malignancy or that other unknown intracellular event prevented the drugs from effectively inhibiting protein production (page 2191, column 1, bridging paragraph; Marshall et al (Clinical Colorectal Cancer, 2004, Vol. 4, pp. 268-274) teach that the administration of ISIS 3521 to patients having metastatic colorectal cancer produced no tumor response and analysis of tumor biopsies showed minimal uptake of the oligonucleotide in the tumor cells (abstract); Oza et al (Gynecological Oncology, 2003, Vol. 89, pp. 129-133) teach that the administration of the 5132 oligonucleotide to patients with recurrent epithelial ovarian cancer produced no response (page 132, first paragraph under the heading "Discussion"). These reference serve to demonstrate that there is no absolute nexus between the inhibition of tumor cells by administration of anti-sense oligonucleotide in a tumor model or in vitro, with the administration of anti-sense oligonucleotides to a patient with a tumor. The specification fails to address the effect of the anti-sense compound on tumor cell in vitro, therefore it would be a burden placed upon applicant to first attempt to ascertain if the mRNA was important to the cancerous phenotype of the cell as questioned by Cripps et al (ibid). the specification fails to provide a dosage schedule, and the plasma level of the administered oligonucleotides which would be commensurate with the appropriate dosage level at the target tissue, nor does the specification address a specific means for attaining the appropriate level within the target tissue that would result in the inhibition of the growth and proliferation of the cancer cells. Because of these deficiencies, one of skill in the art would be subject to undue experimentation without reasonable expectation of success in order to practice the claimed invention.

Applicant argues that the specification has demonstrate efficacy in an art recognized model for human cancer. This has been considered but not fund persuasive. The examiner maintains for the reasons set forth in the rejection above, that animal tumor models do not mimic the situation of a patient with a naturally occurring tumor. Applicant argues that it is within the purview of one of skill in the art to determine the dosage. This has been considered but not found persuasive. The state of the art is lacking teachings for how to provide for the appropriate dosage level in target tissues such that the antisense oligomer is concentrated intracellularly in tumor tissue for the reasons set forth above.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Karen A. Canella, Ph.D.
3/18/2006

KAREN A. CANELLA PH.D
PRIMARY EXAMINER